**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 1. NAME OF THE MEDICINAL PRODUCT

YESCARTA 0.4 – 2 x $10^8$ cells dispersion for infusion

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

### 2.1 General description

YESCARTA (axicabtagene ciloleucel) is a CD19-directed genetically modified autologous T cell immunotherapy. To prepare YESCARTA, patient's own T cells are harvested and genetically modified *ex vivo* by retroviral transduction to express a chimeric antigen receptor (CAR) comprising a murine anti-CD19 single chain variable fragment linked to CD28 co-stimulatory domain and CD3-zeta signalling domain. The anti-CD19 CAR-positive viable T cells are expanded and infused back into the patient, where they can recognise and eliminate CD19-expressing target cells.

### 2.2 Qualitative and quantitative composition

Each patient specific single infusion bag of YESCARTA contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2 x $10^6$ anti-CD19 CAR-positive viable T cells/kg body weight (range: 1 x $10^6$ – 2 x $10^6$ cells/kg), with a maximum of 2 x $10^8$ anti-CD19 CAR T cells.

Excipients with known effect

Each bag of YESCARTA contains 300 mg sodium.

For the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Dispersion for infusion.

A clear to opaque, white to red dispersion.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

YESCARTA is indicated for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL), after two or more lines of systemic therapy.

### 4.2 Posology and method of administration

YESCARTA must be administered in a qualified clinical setting.

YESCARTA therapy should be initiated under the direction of and supervised by a healthcare professional experienced in the treatment of haematological malignancies and trained for administration and management of patients treated with YESCARTA. A minimum of four doses of

tocilizumab for use in the event of cytokine release syndrome (CRS) and emergency equipment must be available prior to infusion of YESCARTA.

Posology

YESCARTA is intended for autologous use only (see section 4.4).

A single dose of YESCARTA contains 2 x $10^6$ CAR-positive viable T cells per kg of body weight (or maximum of 2 x $10^8$ CAR-positive viable T cells for patients 100 kg and above) in approximately 68 mL dispersion in an infusion bag.

The availability of YESCARTA must be confirmed prior to starting the lymphodepleting regimen.

*Pre-treatment (lymphodepleting chemotherapy)*

- A lymphodepleting chemotherapy regimen consisting of cyclophosphamide 500 mg/$m^2$ intravenous and fludarabine 30 mg/$m^2$ intravenous should be administered on the 5$^{th}$, 4$^{th}$, and 3$^{rd}$ day before infusion of YESCARTA.

*Pre-medication*

- Paracetamol 500-1,000 mg given orally and diphenhydramine 12.5 to 25 mg intravenous or oral (or equivalent) approximately 1 hour before YESCARTA infusion is recommended.
- Prophylactic use of systemic corticosteroids is not recommended as it may interfere with the activity of YESCARTA.

*Monitoring*

- Patients should be monitored daily for the first 10 days following infusion for signs and symptoms of potential CRS, neurologic events and other toxicities. Physicians should consider hospitalisation for the first 10 days post infusion or at the first signs or symptoms of CRS and/or neurologic events.
- After the first 10 days following the infusion, the patient should be monitored at the physician's discretion.
- Patients should be instructed to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion.

Special populations

*Patients with human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) infection*

There is no clinical experience in patients with active HIV, HBV or HCV infection.

*Paediatric population*

The safety and efficacy of YESCARTA in children and adolescents below 18 years of age have not yet been established. No data are available.

*Elderly*

No dose adjustment is required in patients ≥ 65 years of age. Efficacy was consistent with the overall treated patient population.

Method of administration

YESCARTA is to be administered via intravenous infusion.

YESCARTA must not be irradiated. Do NOT use a leukodepleting filter.

*Precautions to be taken before handling or administering the medicinal product*
This medicinal product contains genetically modified human blood cells. Healthcare professionals handling YESCARTA should take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases.

*Preparation of YESCARTA*
- Verify that the patient's identity (ID) matches the patient identifiers on the YESCARTA cassette.
- The YESCARTA bag must not be removed from the cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient ID is confirmed, remove the YESCARTA bag from the cassette.
- Check that the patient information on the cassette label matches that on the bag label.
- Inspect the product bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines (or immediately contact Kite).
- Place the infusion bag inside a second sterile bag or per local guidelines.
- Thaw YESCARTA at approximately 37 °C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. YESCARTA should not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.
- Once thawed, YESCARTA is stable at room temperature (20 °C-25 °C) for up to 3 hours.

*Administration*
- For autologous use only.
- Tocilizumab and emergency equipment should be available prior to infusion and during the monitoring period.
- A leukodepleting filter must not be used.
- Central venous access is recommended for the administration of YESCARTA.
- Verify the patient ID again to match the patient identifiers on the YESCARTA bag.
- Prime the tubing with 0.9% sodium chloride solution (0.154 mmol sodium per mL) prior to infusion.
- Infuse the entire content of the YESCARTA bag within 30 minutes by either gravity or a peristaltic pump. YESCARTA is stable at room temperature for up to 3 hours after thaw.
- Gently agitate the bag during YESCARTA infusion to prevent cell clumping.
- After the entire content of the bag is infused, rinse the tubing at the same infusion rate with 0.9% sodium chloride solution (0.154 mmol sodium per mL) to ensure all YESCARTA is delivered.

For special precautions for disposal, see section 6.6.

## 4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Contraindications of the lymphodepleting chemotherapy must be considered.

## 4.4 Special warnings and precautions for use

General

Due to the risks associated with YESCARTA treatment, infusion should be delayed if a patient has any of the following conditions:
- Unresolved serious adverse reactions (especially pulmonary reactions, cardiac reactions, or hypotension) including from preceding chemotherapies.

- Active uncontrolled infection.
- Active graft-versus-host disease (GVHD).

Patients treated with YESCARTA should not donate blood, organs, tissues, and cells for transplantation.

YESCARTA is intended solely for autologous use and must not be administered to other patients. Before infusion, the patient's identity must match the patient identifiers on the YESCARTA infusion bag and cassette. Do not infuse YESCARTA if the information on the patient-specific label does not match the intended patient.

Concomitant disease

Patients with active CNS disorder or inadequate renal, hepatic, pulmonary, or cardiac function are likely to be more vulnerable to the consequences of the adverse reactions described below and require special attention.

Primary central nervous system (CNS) lymphoma

There is no experience of use of YESCARTA in patients with primary CNS lymphoma. Therefore, the risk/benefit of YESCARTA has not been established in this population.

Cytokine release syndrome

Nearly all patients experienced some degree of CRS. Severe CRS, including life-threatening and fatal reactions, was very commonly observed with YESCARTA with a time to onset of 1 to 12 days (see section 4.8).

Ensure that a minimum of 4 doses of tocilizumab, an interleukin-6 (IL-6) receptor inhibitor, are available for each patient prior to infusion of YESCARTA.

Monitor patients daily for signs and symptoms of CRS for at least 10 days following infusion at the qualified clinical facility. After the first 10 days following infusion, the patient should be monitored at the physician's discretion.

Counsel patients to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion and to seek immediate medical attention should signs or symptoms of CRS occur. Treatment algorithms have been developed to ameliorate some of the CRS symptoms experienced by patients on YESCARTA. These include the use of tocilizumab or tocilizumab and corticosteroids for moderate, severe, or life-threatening CRS as summarised in Table 1. Patients who experience Grade 2 or higher CRS (e.g. hypotension, not responsive to fluids, or hypoxia requiring supplemental oxygenation) should be monitored with continuous cardiac telemetry and pulse oximetry. For patients experiencing severe CRS, consider performing an echocardiogram to assess cardiac function. For severe or life-threatening CRS, consider intensive-care supportive therapy.

YESCARTA should not be administered to patients with active infections or inflammatory disease until these conditions have resolved.

CRS has been known to be associated with end organ dysfunction (e.g., hepatic, renal, cardiac, and pulmonary). In addition worsening of underlying organ pathologies can occur in the setting of CRS. Patients with medically significant cardiac dysfunction should be managed by standards of critical care and measures such as echocardiography should be considered.

Diagnosis of CRS requires excluding alternate causes of systemic inflammatory response, including infection. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

Evaluation for haemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS) should be considered in patients with severe or unresponsive CRS.

YESCARTA continues to expand and persist following administration of tocilizumab and corticosteroids. Tumour necrosis factor (TNF) antagonists are not recommended for management of YESCARTA-associated CRS.

**Table 1: CRS grading and management guidance**

| **CRS Grade *(a)*** | **Tocilizumab** | **Corticosteroids** |
|---|---|---|
| **Grade 1**<br>Symptoms require symptomatic treatment only (e.g., fever, nausea, fatigue, headache, myalgia, malaise). | N/A | N/A |
| **Grade 2**<br>Symptoms require and respond to moderate intervention. Oxygen requirement less than 40% $FiO_2$ or hypotension responsive to fluids or low dose of one vasopressor or Grade 2 organ toxicity *(b).* | Administer tocilizumab *(c)* 8 mg/kg intravenously over 1 hour (not to exceed 800 mg).<br>Repeat tocilizumab every 8 hours as needed if not responsive to intravenous fluids or increasing supplemental oxygen. Limit to a maximum of 3 doses in a 24 hour period; maximum total of 4 doses if no clinical improvement in the signs and symptoms of CRS. | Manage per Grade 3 if no improvement within 24 hours after starting tocilizumab. |
| **Grade 3**<br>Symptoms require and respond to aggressive intervention. Oxygen requirement greater than or equal to 40% $FiO_2$ or hypotension requiring high-dose or multiple vasopressors or Grade 3 organ toxicity or Grade 4 transaminitis. | Per Grade 2 | Administer methylprednisolone 1 mg/kg intravenously twice daily or equivalent dexamethasone (e.g., 10 mg intravenously every 6 hours).<br>Continue corticosteroids use until the event is Grade 1 or less, then taper over 3 days.<br>If not improving, manage as Grade 4 (below). |
| **Grade 4**<br>Life-threatening symptoms. Requirements for ventilator support or continuous veno-venous haemodialysis or Grade 4 organ toxicity (excluding transaminitis). | Per Grade 2 | Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above.<br><br>Consider alternate immunosuppressants if no improvement or if condition worsens. |

N/A = not available/not applicable
*(a) Lee et al 2014.*
*(b) Refer to Table 2 for management of neurologic adverse reactions.*
*(c) Refer to tocilizumab summary of product characteristics for details.*

Neurologic adverse reactions

Severe neurologic adverse reactions have been very commonly observed in patients treated with YESCARTA, which could be life-threatening or fatal (see section 4.8). Patients with a history of CNS disorders such as seizures or cerebrovascular ischaemia may be at increased risk. Fatal and serious cases of cerebral oedema have been reported in patients treated with YESCARTA. Patients should be monitored for signs and symptoms of neurologic adverse reactions (Table 2). Patients should be monitored at least daily for 10 days at the qualified healthcare facility following infusion for signs and symptoms of neurologic toxicity. After the first 10 days following the infusion, the patient should be monitored at the physician's discretion. Counsel patients to remain within proximity of a qualified clinical facility for at least 4 weeks following infusion and to seek immediate medical attention should

signs or symptoms of neurologic toxicity occur. Monitoring of vital signs and organ functions should be considered depending on the severity of the reaction.

Patients who experience Grade 2 or higher neurologic toxicities should be monitored with continuous cardiac telemetry and pulse oximetry. Provide intensive-care supportive therapy for severe or life-threatening neurologic toxicities. Non-sedating, anti-seizure medicines should be considered as clinically indicated for Grade 2 or higher adverse reactions. Treatment algorithms have been developed to ameliorate the neurologic adverse reactions experienced by patients on YESCARTA. These include the use of tocilizumab (if concurrent CRS) and/or corticosteroids for moderate, severe, or life-threatening neurologic adverse reactions as summarised in Table 2.

**Table 2: Neurologic adverse reaction grading and management guidance**

| **Grading assessment** | **Concurrent CRS** | **No concurrent CRS** |
|---|---|---|
| Grade 2 | Administer tocilizumab per Table 1 for management of Grade 2 CRS.<br>If no improvement within 24 hours after starting tocilizumab, administer dexamethasone 10 mg intravenously every 6 hours if not already taking other corticosteroids. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days. | Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days. |
| | Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. | |
| Grade 3 | Administer tocilizumab per Table 1 for management of Grade 2 CRS.<br>In addition, administer dexamethasone 10 mg intravenously with the first dose of tocilizumab and repeat dose every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days. | Administer dexamethasone 10 mg intravenously every 6 hours. Continue dexamethasone use until the event is Grade 1 or less, then taper over 3 days. |
| | Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. | |
| Grade 4 | Administer tocilizumab per Table 1 for management of Grade 2 CRS.<br>Administer methylprednisolone 1000 mg intravenously per day with first dose of tocilizumab and continue methylprednisolone 1000 mg intravenously per day for 2 more days; if improves, then manage as above. | Administer methylprednisolone 1000 mg intravenously per day for 3 days; if improves, then manage as above. |
| | Consider non-sedating, anti-seizure medicines (e.g., levetiracetam) for seizure prophylaxis. | |

Infections and febrile neutropenia

Serious infections have been very commonly observed with YESCARTA (see section 4.8). Patients should be monitored for signs and symptoms of infection before, during, and after YESCARTA infusion and treated appropriately. Prophylactic anti-microbials should be administered according to standard institutional guidelines.

Febrile neutropenia has been observed in patients after YESCARTA infusion (see section 4.8) and may be concurrent with CRS. In the event of febrile neutropenia, evaluate for infection and manage with broad spectrum antibiotics, fluids, and other supportive care as medically indicated.

HBV reactivation

HBV reactivation, in some cases resulting in fulminant hepatitis, hepatic failure, and death, can occur in patients treated with drugs directed against B cells. Screening for HBV, HCV, and HIV should be performed in accordance with clinical guidelines before collection of cells for manufacturing of YESCARTA.

Prolonged cytopenias

Patients may exhibit cytopenias for several weeks following lymphodepleting chemotherapy and YESCARTA infusion. Grade 3 or higher prolonged cytopenias following YESCARTA infusion occurred very commonly and included thrombocytopenia, neutropenia, and anaemia. Monitor blood counts after YESCARTA infusion.

Hypogammaglobulinaemia

B-cell aplasia leading to hypogammaglobulinaemia can occur in patients receiving treatment with YESCARTA. Hypogammaglobulinaemia has been very commonly observed in patients treated with YESCARTA. Immunoglobulin levels should be monitored after treatment with YESCARTA and managed using infection precautions, antibiotic prophylaxis, and immunoglobulin replacement.

Hypersensitivity reactions

Allergic reactions may occur with the infusion of YESCARTA. Serious hypersensitivity reactions including anaphylaxis, may be due to dimethyl sulfoxide (DMSO) or residual gentamicin in YESCARTA.

Secondary malignancies

Patients treated with YESCARTA may develop secondary malignancies. Monitor patients life-long for secondary malignancies. In the event that a secondary malignancy occurs, contact the company to obtain instructions on patient samples to collect for testing.

Tumour lysis syndrome (TLS)

TLS, which may be severe, has occasionally been observed. To minimise risk of TLS, patients with elevated uric acid or high tumour burden should receive allopurinol, or an alternative prophylaxis, prior to YESCARTA infusion. Signs and symptoms of TLS should be monitored and events managed according to standard guidelines.

Prior treatment with anti-CD19 therapy

There is limited experience with YESCARTA in patients exposed to prior CD19-directed therapy. YESCARTA is not recommended if the patient has relapsed with CD19-negative disease after prior anti-CD19 therapy.

Excipients

This medicinal product contains 300 mg sodium per infusion, equivalent to 15% of the WHO recommended maximum daily intake of 2 g sodium for an adult.

## 4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed with YESCARTA.

Live vaccines

The safety of immunisation with live viral vaccines during or following YESCARTA treatment has not been studied. Vaccination with live virus vaccines is not recommended for at least 6 weeks prior to the start of lymphodepleting chemotherapy, during YESCARTA treatment, and until immune recovery following treatment with YESCARTA.

## 4.6 Fertility, pregnancy and lactation

Women of childbearing potential/Contraception

The pregnancy status of women of child bearing potential must be verified before starting YESCARTA treatment.

See the prescribing information for lymphodepleting chemotherapy for information on the need for effective contraception in patients who receive the lymphodepleting chemotherapy.

There are insufficient exposure data to provide a recommendation concerning duration of contraception following treatment with YESCARTA.

Pregnancy

There are no available data with YESCARTA use in pregnant women. No reproductive and developmental toxicity animal studies have been conducted with YESCARTA to assess whether it can cause foetal harm when administered to a pregnant woman (see section 5.3).

It is not known if YESCARTA has the potential to be transferred to the foetus. Based on the mechanism of action, if the transduced cells cross the placenta, they may cause foetal toxicity, including B-cell lymphocytopenia. Therefore, YESCARTA is not recommended for women who are pregnant, or for women of childbearing potential not using contraception. Pregnant women should be advised on the potential risks to the foetus. Pregnancy after YESCARTA therapy should be discussed with the treating physician.

Assessment of immunoglobulin levels and B-cells in newborns of mothers treated with YESCARTA should be considered.

Breast-feeding

It is unknown whether YESCARTA is excreted in human milk or transferred to the breast-feeding child. Breast-feeding women should be advised of the potential risk to the breast-fed child.

Fertility

No clinical data on the effect of YESCARTA on fertility are available. Effects on male and female fertility have not been evaluated in animal studies.

## 4.7 Effects on ability to drive and use machines

YESCARTA has major influence on the ability to drive and use machines. Due to the potential for neurologic events, including altered mental status or seizures, patients should refrain from driving or operating heavy or potentially dangerous machines until at least 8 weeks after infusion or until resolution of neurologic adverse reactions.

## 4.8 Undesirable effects

Summary of the safety profile

The safety data described in this section reflect exposure to YESCARTA in ZUMA-1, a Phase 1/2 study in which 108 patients with relapsed/refractory B-cell non-Hodgkin lymphoma (NHL) received CAR-positive T cells based on a recommended dose which was weight-based. The median duration of follow up was 27.4 months.

The most significant and frequently occurring adverse reactions were CRS (93%), encephalopathy (58%), and infections (39%).

Serious adverse reactions occurred in 56% of patients. The most common serious adverse reactions included encephalopathy (22%), unspecified pathogen infections (16%), bacterial infections (6%), febrile neutropenia (6%), viral infections (5%), and pyrexia (5%).

The most common Grade 3 or higher adverse reactions included encephalopathy (31%), unspecified pathogen infections (19%), CRS (11%), bacterial infection (9%), aphasia (7%), viral infection (6%), delirium (6%), hypotension (6%), and hypertension (6%).

Tabulated list of adverse reactions

Adverse reactions reported from clinical trials and post-marketing setting are presented below. These reactions are presented by system organ class and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

**Table 3: Adverse drug reactions identified with YESCARTA**

| **System Organ Class (SOC)** | **Frequency** | **Adverse reactions** |
|---|---|---|
| Infections and infestations | | |
| | Very common | Unspecified pathogen infections<br>Viral infections<br>Bacterial infections |
| | Common | Fungal infections |
| Blood and lymphatic system disorders | | |
| | Very common | Leukopenia<br>Neutropenia<br>Anaemia<br>Thrombocytopenia |
| | Common | Coagulopathy |
| Immune system disorders | | |
| | Very common | Cytokine Release Syndrome<br>Hypogammaglobulinaemia |
| | Common | Hypersensitivity<br>Histiocytosis Haematophagic |
| Metabolism and nutrition disorders | | |
| | Very common | Dehydration<br>Decreased appetite<br>Hypophosphataemia<br>Hyponatraemia<br>Weight decrease |
| | Common | Hypocalcaemia<br>Hypoalbuminaemia |
| Psychiatric disorders | | |
| | Very common | Delirium<br>Anxiety |
| | Common | Insomnia |
| Nervous system disorders | | |
| | Very common | Encephalopathy<br>Headache<br>Tremor<br>Dizziness<br>Aphasia |
| | Common | Ataxia<br>Neuropathy<br>Seizure<br>Dyscalculia<br>Myoclonus |

| System Organ Class (SOC) | Frequency | Adverse reactions |
|---|---|---|
| | Uncommon | Spinal cord oedema<br>Myelitis<br>Quadriplegia |
| Cardiac disorders | | |
| | Very common | Tachycardia<br>Arrhythmia |
| | Common | Cardiac arrest<br>Cardiac failure |
| Vascular disorders | | |
| | Very common | Hypotension<br>Hypertension |
| | Common | Thrombosis<br>Capillary leak syndrome |
| Respiratory, thoracic and mediastinal disorders | | |
| | Very common | Cough<br>Dyspnoea<br>Hypoxia<br>Pleural effusion |
| | Common | Pulmonary oedema |
| Gastrointestinal disorders | | |
| | Very common | Diarrhoea<br>Nausea<br>Vomiting<br>Constipation<br>Abdominal pain<br>Dry mouth |
| | Common | Dysphagia* |
| Skin and subcutaneous tissue disorders | | |
| | Common | Rash |
| Musculoskeletal and connective tissue disorders | | |
| | Very common | Motor dysfunction<br>Pain in extremity<br>Back pain<br>Arthralgia<br>Muscle pain |
| Renal and urinary disorders | | |
| | Common | Renal insufficiency |
| General disorders and administration site conditions | | |
| | Very common | Fatigue<br>Pyrexia<br>Oedema<br>Chills |
| Investigations | | |
| | Very common | Alanine aminotransferase increased<br>Aspartate aminotransferase increased |
| | Common | Bilirubin increased |

Only cytopenias that resulted in (i) new or worsening clinical sequelae or (ii) that required therapy or (iii) adjustment in current therapy are included in Table 3.

* Dysphagia has been reported in the setting of neurologic toxicity and encephalopathy

Description of selected adverse reactions

*Cytokine release syndrome*

CRS occurred in 93% of patients. Eleven percent (11%) of patients experienced Grade 3 or higher (severe, life-threatening, and fatal) CRS. The median time to onset was 2 days (range: 1 to 12 days) and the median duration was 7 days (range: 2 to 29 days). Ninety-eight percent (98%) of patients recovered from CRS.

The most common signs or symptoms associated with CRS included pyrexia (83%), hypotension (44%), tachycardia (24%), hypoxia (23%), and chills (20%). Serious adverse reactions that may be associated with CRS included acute kidney injury, atrial fibrillation, ventricular tachycardia, cardiac arrest, cardiac failure, capillary leak syndrome, hypotension, hypoxia, and HLH/MAS. See section 4.4 for monitoring and management guidance.

*Neurologic adverse reactions*
Neurologic adverse reactions occurred in 67% of patients. Thirty-two percent (32%) of patients experienced Grade 3 or higher (severe or life-threatening) adverse reactions. The median time to onset was 5 days (range: 1 to 17 days). The median duration was 13 days (range: 1 to 191 days). Most patients recovered from neurologic adverse reactions, with the exception of 4 patients who had ongoing neurologic adverse reactions at the time of death; the deaths were due to other causes.

The most common signs or symptoms associated with neurologic adverse reactions included encephalopathy (58%), headache (40%), tremor (31%), dizziness (21%), aphasia (18%), and delirium (17%). Serious adverse reactions including encephalopathy (22%), aphasia (4%), delirium (4%), and seizures (1%) have been reported in patients administered YESCARTA.

Other neurologic adverse reactions have been reported less frequently in clinical trials and included dysphagia (5%), myelitis (0.2%), and quadriplegia (0.2%).

Spinal cord oedema was reported, in the context of neurologic toxicity in the post-marketing setting.

See section 4.4 for monitoring and management guidance.

*Febrile neutropenia and infections*
Febrile neutropenia was observed in 36% of patients after YESCARTA infusion. Infections occurred in 39% of patients in ZUMA-1. Grade 3 or higher (severe, life-threatening, or fatal) infections occurred in 26% of patients. Grade 3 or higher unspecified pathogen, bacterial, and viral infections occurred in 19%, 9%, and 6% of patients respectively. The most common site of infection was in the respiratory tract. See section 4.4 for monitoring and management guidance.

*Prolonged cytopenias*
Grade 3 or higher neutropenia (including febrile neutropenia), anaemia, and thrombocytopenia occurred in 80%, 45%, and 40% of patients, respectively. Prolonged (still present at Day 30 or with an onset at Day 30 or beyond) Grade 3 or higher neutropenia, thrombocytopenia, and anaemia occurred in 26%, 24%, and 10% of patients, respectively. Grade 3 or higher neutropenia, thrombocytopenia, and anaemia present after Day 93 occurred in 11%, 7%, and 3% of patients, respectively. See section 4.4 for management guidance.

*Hypogammaglobulinaemia*
In ZUMA-1, hypogammaglobulinaemia occurred in 16% of patients. Cumulatively, 33 (31%) of 108 subjects received intravenous immunoglobulin therapy at the time of the 24-month analysis. See section 4.4 for management guidance.

Immunogenicity

The immunogenicity of YESCARTA has been evaluated using an enzyme-linked immunosorbent assay (ELISA) for the detection of binding antibodies against FMC63, the originating antibody of the anti-CD19 CAR. Three patients tested positive for anti-FMC63 prior to being treated with YESCARTA. An impact of these antibodies on efficacy or safety was not discernible.

Special population

There is limited experience with YESCARTA in patients ≥ 75 years of age. Generally, safety and efficacy were similar between patients ≥ 65 years and patients < 65 years of age treated with

YESCARTA. Outcomes were consistent between patients with Eastern Cooperative Oncology Group (ECOG) of 0 and 1 and by sex.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

### 4.9 Overdose

There are no data regarding the signs of overdose with YESCARTA.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other antineoplastic agents, ATC code: not yet assigned

Mechanism of action

YESCARTA, an engineered autologous T-cell immunotherapy product, binds to CD19 expressing cancer cells and normal B cells. Following anti-CD19 CAR T-cell engagement with CD19 expressing target cells, the CD28 and CD3-zeta co-stimulatory domains activate downstream signalling cascades that lead to T-cell activation, proliferation, acquisition of effector functions, and secretion of inflammatory cytokines and chemokines. This sequence of events leads to apoptosis and necrosis of CD19-expressing target cells.

Pharmacodynamic effects

In phase 2 of ZUMA-1, after YESCARTA infusion, pharmacodynamic responses were evaluated over a 4-week interval by measuring transient elevation of cytokines, chemokines, and other molecules in blood. Levels of cytokines and chemokines such as IL-6, IL-8, IL-10, IL-15, TNF-α, IFN-γ, and IL2Rα were analyzed. Peak elevation was observed within the first 14 days after infusion, and levels generally returned to baseline within 28 days.

Due to the on-target, off-tumour effect of YESCARTA, a period of B-cell aplasia is expected following treatment. Among 73 patients with evaluable samples at baseline, 40% had detectable B-cells; the B-cell aplasia observed in the majority of patients at baseline was attributed to prior therapies. Following YESCARTA treatment, the proportion of patients with detectable B-cells decreased: 20% had detectable B-cells at Month 3, and 22% had detectable B-cells at Month 6. The initiation of B-cell recovery was first noted at Month 9, when 56% of patients had detectable B-cells. This trend of B-cell recovery continued over time, as 64% of patients had detectable B-cells at Month 18, and 77% of patients had detectable B-cells at Month 24. Patients were not required to be followed after they progressed; thus, the majority of patients with evaluable samples were responders.

Analyses performed to identify associations between cytokine levels and incidence of CRS or neurologic events showed that higher levels (peak and AUC at 1 month) of IL-15, as well as IL-6, were associated with Grade 3 or higher neurologic adverse reactions and Grade 3 or higher CRS.

Clinical efficacy and safety

*DLBCL, PMBCL and DLBCL arising from follicular lymphoma (ZUMA-1)*

A total of 108 patients were treated with YESCARTA in a phase 1/2 open-label, multicentre, single-arm study in patients with relapsed or refractory aggressive B-cell NHL. Efficacy was based on 101 patients in phase 2, including histologically confirmed DLBCL (N = 77), PMBCL (N = 8), or DLBCL arising from follicular lymphoma, (N = 16) based on the 2008 WHO-classification. DLBCL in ZUMA-1 included patients with DLBCL NOS, other DLBCL subtypes, and high-grade B-cell lymphoma (HGBCL) based on the 2016 WHO-classification. Forty-seven patients were evaluable for MYC, BCL-2, and BCL-6 status. Thirty were found to have double expressor DLBCL (overexpression of both MYC and BCL-2 protein); 5 were found to have HGBCL with MYC, BCL-2 or BCL-6 gene rearrangement (double- and triple-hit); and 2 were found to have HGBCL not otherwise specified. Sixty-six patients were evaluable for cell-of-origin classifications (germinal center B-cell type [GCB] or activated B-cell type [ABC]). Of these, 49 patients had GCB-type and 17 patients had ABC-type.

Eligible patients were ≥ 18 years of age with refractory disease defined as progressive disease (PD) or stable disease (SD) as best response to last line of therapy, or disease progression within 12 months after autologous stem cell transplant (ASCT). Patients who were refractory to chemotherapy or who relapsed after two or more lines of systemic therapy were generally ineligible for haematopoietic stem cell transplantation. Patients must have received at least prior anti-CD20 antibody therapy and an anthracycline containing regimen. Patients with CNS lymphoma, a history of allogeneic stem cell transplantation (SCT) or prior anti-CD19 CAR or other genetically modified T-cell therapy were excluded. Patients with a history of CNS disorders (such as seizures or cerebrovascular ischemia), cardiac ejection fraction of less than 50% or room air oxygen saturation of less than 92%, or autoimmune disease requiring systemic immunosuppression were ineligible. The median duration of follow up was 27.1 months (still ongoing). A summary of the patient demographics is provided in Table 4.

**Table 4: Summary of demographics for ZUMA-1 phase 2 (12 month analysis)**

| **Category** | **All leukapheresed (ITT) Cohort 1 + 2 (N = 111)** | **All treated (mITT) Cohort 1 + 2 (N = 101)** |
|---|---|---|
| *Age (years)* | | |
| Median (min, max) | 58 (23, 76) | 58 (23, 76) |
| ≥ 65 | 23% | 24% |
| Male gender | 69% | 67% |
| *Race* | | |
| White | 85% | 86% |
| Asian | 4% | 3% |
| Black | 4% | 4% |
| *ECOG status* | | |
| ECOG 0 | 41% | 42% |
| ECOG 1 | 59% | 58% |
| Median number of prior therapies (min, max) | 3 (1, 10) | 3 (1, 10) |
| Patients with refractory disease to ≥ 2 prior lines of therapy | 77% | 76% |
| Patients relapsed within 1 year of ASCT | 20% | 21% |
| Patients with International Prognostic Index 3/4 | 46% | 46% |
| Patients with disease stage III/IV | 85% | 85% |

YESCARTA was administered as a single infusion at a target dose of 2 x $10^6$ anti-CD19 CAR T cells/kg after lymphodepleting chemotherapy regimen of 500 mg/$m^2$ intravenous cyclophosphamide and 30 mg/$m^2$ intravenous fludarabine on the 5$^{th}$, 4$^{th}$, and 3$^{rd}$ day before YESCARTA. Bridging chemotherapy between leukapheresis and lymphodepleting chemotherapy was not permitted. All patients were hospitalized for observation for a minimum of 7 days after YESCARTA infusion.

Of 111 patients who underwent leukapheresis, 101 received YESCARTA. Nine patients were not treated, primarily due to progressive disease or serious adverse events after enrolment and prior to cell delivery. One out of 111 patients did not receive the product due to manufacturing failure. The median time from leukapheresis to product delivery was 17 days (range: 14 to 51 days), and the median time from leukapheresis to infusion was 24 days (range: 16 to 73 days). The median dose was $2.0 \times 10^6$ anti-CD19 CAR T cells/kg. ITT was defined as all patients who underwent leukapheresis; mITT was defined as all patients who received YESCARTA.

The primary endpoint was objective response rate (ORR). Secondary endpoints included duration of response (DOR), overall survival (OS), and severity of adverse events. The ORR was prespecified to be tested in the first 92 treated patients and was significantly higher than the prespecified rate of 20% ($P < 0.0001$).

In the primary analysis, based on the mITT population (minimum follow up of 6 months) the ORR was 72% and the complete response (CR) rate was 51%, as determined by an independent review committee. In the 12-month follow-up analysis (Table 5), the ORR was 72% and the CR rate was 51%. The median time to response was 1.0 months (range: 0.8 to 6.3 months). The DOR was longer in patients who achieved CR, as compared to patients with a best response of partial response (PR). Of the 52 patients who achieved CR, 7 patients had SD and 9 had PR at their initial tumour assessment and converted to CR as late as 6.5 months. The ORR results within PMBCL and DLBCL arising from follicular lymphoma were both 88%. CR rates were 75% and 56%, respectively. Of the 111 patients in the ITT population, the ORR was 66% and the CR was 47%. Other outcomes were consistent with those of the mITT population.

In the 24-month follow-up analysis, based on the mITT population (results from an independent review committee), the ORR and the CR rate were 74% and 54%, respectively. The median time to response was 1.0 months (range: 0.8 to 12.2 months). The DOR was longer in patients who achieved CR compared to patients with a best response of PR (Table 5). Of the 55 patients who achieved CR, 7 patients had SD and 10 had PR at their initial tumour assessment and converted to CR as late as 12 months after YESCARTA infusion. Median duration of response and median overall survival have not been reached (Table 5).

In the phase 1 part of ZUMA-1, 7 patients were treated. Five patients responded, including 4 CRs. At the 12-month follow-up analysis, 3 patients remained in CR 24 months after YESCARTA infusion. At the 24-month follow-up analysis, these 3 patients remained in CR at 30 to 35 months after YESCARTA infusion.

**Table 5. Summary of efficacy results for ZUMA-1 phase 2**

| **Category** | **All leukapheresed (ITT) Cohort 1 + 2 (N = 111)** | | **All treated (mITT) Cohort 1 + 2 (N = 101)** | |
|---|---|---|---|---|
| | **12-month analysis** | **24-month analysis** | **12-month analysis** | **24-month analysis** |
| ORR (%) [95% CI] | 66 (56, 75) | 68 (58, 76) | 72 (62, 81) | 74 (65, 82) |
| CR (%) | 47 | 50 | 51 | 54 |
| Duration of Response[a], median (range) in months | 14.0 (0.0, 17.3) | NE (0.0, 29.5) | 14.0 (0.0, 17.3) | NE (0.0, 29.5) |
| Duration of Response[a], CR, median (range) in months | NE (0.4, 17.3) | NE (0.4, 29.5) | NE (0.4, 17.3) | NE (0.4, 29.5) |
| Overall Survival, median (months) [95% CI] | 17.4 (11.6, NE) | 17.4 (11.6, NE) | NE (12.8, NE) | NE (12.8, NE) |
| 6 month OS (%) [95% CI] | 81.1 (72.5, 87.2) | 81.1 (72.5, 87.2) | 79.2 (69.9, 85.9) | 79.2 (69.9, 85.9) |
| 9 month OS (%) [95% CI] | 69.4 (59.9, 77.0) | 69.4 (59.9, 77.0) | 69.3 (59.3, 77.3) | 69.3 (59.3, 77.3) |
| 12 month OS (%) [95% CI] | 59.3 (49.6, 67.8) | 59.5 (49.7, 67.9) | 60.4 (50.2, 69.2) | 60.4 (50.2, 69.2) |

| Category | All leukapheresed (ITT) Cohort 1 + 2 (N = 111) | | All treated (mITT) Cohort 1 + 2 (N = 101) | |
|---|---|---|---|---|
| | 12-month analysis | 24-month analysis | 12-month analysis | 24-month analysis |
| ORR (%) [95% CI] | 66 (56, 75) | 68 (58, 76) | 72 (62, 81) | 74 (65, 82) |
| 24 month OS (%) [95% CI] | Not applicable | 47.7 (38.2, 56.7) | Not applicable | 50.5 (40.4, 59.7) |

NE= Not estimable (not reached)

a Duration of response was censored at the time of SCT for subjects who received SCT while in response.

Note: The 12-month analysis had a median follow-up of 15.1 months. The 24-month analysis had a median follow-up of 27.1 months. OS relates to the time from the leukapheresis date (ITT) or YESCARTA infusion (mITT) to death from any cause.

*SCHOLAR-1*
A retrospective, patient-level, pooled analysis of outcomes in refractory aggressive NHL (N = 636) was conducted (Crump et al., 2017) to provide confirmation of the prespecified control response rate of 20% and historical context for interpreting the ZUMA-1 results. The analysis included patients who had not responded (SD or PD) to their last line of therapy, or had relapsed within 12 months after ASCT. Response and survival after treatment with available standard-of-care therapy was evaluated. The ORR was 26% [95% CI (21, 31)] and the CR rate was 7% [95% CI (3, 15)], with a median OS of 6.3 months.

## 5.2 Pharmacokinetic properties

Peak levels of anti-CD19 CAR T cells occurred within the first 8 to 15 days after YESCARTA infusion. The median peak level of anti-CD19 CAR T cells in the blood ($C_{max}$) was 38.3 cells/µL (range: 0.8 to 1513.7 cells/µL), which decreased to a median of 2.1 cells/µL by 1 month (range: 0 to 167.4 cells/µL) and to a median of 0.4 cells/µL by 3 months (range: 0 to 28.4 cells/µL) after YESCARTA infusion.

Age (range: 23 to 76 years) and sex had no significant impact on AUC and $C_{max}$ of YESCARTA.

The number of anti-CD19 CAR T cells in the blood was positively associated with objective response (CR or PR). The median anti-CD19 CAR T cell $C_{max}$ level in responders (N = 71) was 216% higher compared to the corresponding level in nonresponders (N = 25) (43.6 cells/µL *versus* 20.2 cells/µL). Median $AUC_{Day\ 0\text{-}28}$ in responding patients (N = 71) was 253% of the corresponding level in nonresponders (N = 25) (562.0 days x cells/µL *versus* 222.0 days x cells/µL).

YESCARTA comprises human autologous T cells. The anticipated metabolic products are typical cellular degradation products resulting from normal cellular clearance mechanisms. Thus, the infused CAR T cells are expected to be cleared over time. Anti-CD19 CAR T cell levels decreased toward background levels by Month 3 after infusion.
Studies of YESCARTA in patients with hepatic and renal impairment were not conducted.

## 5.3 Preclinical safety data

YESCARTA comprises engineered human T cells, therefore there are no representative *in vitro* assays, *ex vivo* models, or *in vivo* models that can accurately address the toxicological characteristics of the human product. Hence, traditional toxicology studies used for drug development were not performed.

No carcinogenicity or genotoxicity studies have been conducted with YESCARTA.

No studies have been conducted to evaluate the effects of YESCARTA on fertility, reproduction, and development.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Cryostor CS10
Sodium chloride
Human albumin

## 6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

### 6.3 Shelf life

YESCARTA is stable for 1 year when stored frozen in the vapour phase of liquid nitrogen (≤ -150 ˚C).

The stability of YESCARTA upon completion of thawing is up to 3 hours at room temperature (20 ˚C to 25 °C). However, YESCARTA infusion should begin within 30 minutes of thaw completion and the total YESCARTA infusion time should not exceed 30 minutes. Thawed product should not be refrozen.

### 6.4 Special precautions for storage

YESCARTA bags must be stored in the vapour phase of liquid nitrogen (≤ -150 ˚C) and YESCARTA must remain frozen until the patient is ready for treatment to ensure viable live autologous cells are administered to the patient.

For storage conditions after thawing of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container

Ethylene-vinyl acetate cryostorage bag with sealed addition tube and two available spike ports, containing approximately 68 mL of cell dispersion.

One cryostorage bag is individually packed in a shipping cassette.

### 6.6 Special precautions for disposal and other handling

Irradiation could lead to inactivation of the product.

Precautions to be taken for the disposal of the medicinal product

YESCARTA contains genetically modified human blood cells. Local biosafety guidelines should be followed for unused medicinal products or waste material. All material that has been in contact with YESCARTA (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local biosafety guidelines.

## 7. MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
Science Park 408
1098 XH Amsterdam
The Netherlands

## 8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1299/001

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23 August 2018

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

**ANNEX II**

**A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Kite Pharma, Inc.
2355 Utah Avenue
El Segundo
California
CA 90245
United States

Name and address of the manufacturers responsible for batch release

Lonza Netherlands B.V.
Oxfordlaan 70
6229EV Maastricht
The Netherlands

Kite Pharma EU B.V.
Science Park 406
1098 XH Amsterdam
The Netherlands

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Key elements:

**Availability of tocilizumab and site qualification**

To minimise the risks associated with the treatment of YESCARTA, the MAH must ensure that hospitals and their associated centres that dispense YESCARTA are specially qualified in accordance with the agreed control distribution program.

The MAH must ensure on-site, immediate access to 4 doses of tocilizumab for each patient as CRS management medication prior to treating patients.

YESCARTA will only be supplied to hospitals and associated centres that are qualified and only if the healthcare professionals involved in the treatment of a patient have completed the educational program.

**Educational program** – Prior to the launch of YESCARTA in each Member State the MAH must agree the content and format of the educational materials with the National Competent Authority.

HCP Educational program

The MAH shall ensure that in each Member State where YESCARTA is marketed, all HCPs who are expected to prescribe, dispense, and administer YESCARTA shall be provided with a guidance document to:

- facilitate identification of CRS and serious neurologic adverse reactions
- facilitate management of the CRS and serious neurologic adverse reactions
- ensure adequate monitoring of CRS and serious neurologic adverse reactions
- facilitate provision of all relevant information to patients
- ensure that adverse reactions are adequately and appropriately reported
- ensure that detailed instructions about the thawing procedure are provided
- before treating a patient, ensure that 4 doses of tocilizumab for each patient are available on site

Patient Educational program

To inform and explain to patients

- the risks of CRS and serious neurologic adverse reactions, associated with YESCARTA
- the need to report the symptoms to their treating doctor immediately
- the need to remain in the proximity of the location where YESCARTA was received for at least 4 weeks following YESCARTA infusion
- the need to carry the patient alert card at all times

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

| Description | Due date |
|---|---|
| Non-interventional post-authorisation safety study (PASS): In order to assess the safety profile including long term safety in patients with B-lymphocyte malignancies treated with axicabtagene ciloleucel in the post marketing setting, the applicant should conduct and submit a study based on a registry. | •Update reports:<br>Annual safety reports and<br>5-yearly interim reports<br>•Final report of study results:<br>December 2038 |

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CONTAINER (CASSETTE)**

## 1. NAME OF THE MEDICINAL PRODUCT

YESCARTA 0.4 – 2 x $10^8$ cells dispersion for infusion
axicabtagene ciloleucel (CAR+ viable T cells)

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor (CAR) with a target dose of 2 x $10^6$ anti-CD19 CAR-positive viable T cells/kg.

## 3. LIST OF EXCIPIENTS

Excipients: Cryostor CS10, human albumin, sodium chloride. See leaflet for further information.

## 4. PHARMACEUTICAL FORM AND CONTENTS

Dispersion for infusion
One sterile infusion bag.
Contents: approximately 68 mL of cell dispersion.

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Do not irradiate.
For intravenous use only.
Gently mix the contents of the bag while thawing.
Do NOT use a leukodepleting filter.
STOP confirm patient ID prior to infusion.

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

For autologous use only.

## 8. EXPIRY DATE

EXP:

## 9. SPECIAL STORAGE CONDITIONS

Store frozen in vapour phase of liquid nitrogen ≤ -150˚C.
Do not refreeze.

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

This medicine contains genetically-modified cells.
Unused medicine must be disposed of in compliance with the local biosafety guidelines.

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Kite Pharma EU B.V.
Science Park 408
1098 XH Amsterdam
The Netherlands

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1299/001

## 13. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Kite Patient ID:
Additional Patient ID:
Patient Name:
Patient DOB:

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

## 17. UNIQUE IDENTIFIER – 2D BARCODE

Not applicable

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

Not applicable

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**INFUSION BAG**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

YESCARTA 0.4 – 2 x $10^8$ cells dispersion for infusion
axicabtagene ciloleucel (CAR+ viable T cells)
For intravenous use only.

## 2. METHOD OF ADMINISTRATION

## 3. EXPIRY DATE

EXP:

## 4. BATCH NUMBER, DONATION AND PRODUCT CODES

Lot:
Kite Patient ID:
Additional Patient ID:
Patient Name:
Patient DOB:

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

One sterile infusion bag.
Contents: approximately 68 mL of cell dispersion.

## 6. OTHER

For autologous use only.
Verify patient ID.

# B. PACKAGE LEAFLET

**Package leaflet: Information for the patient**

**YESCARTA 0.4 – 2 x $10^8$ cells dispersion for infusion**
axicabtagene ciloleucel (CAR+ viable T cells)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you are given this medicine because it contains important information for you.**
- Keep this leaflet. You may need to read it again.
- Your doctor will give you a Patient Alert Card. Read it carefully and follow the instructions on it.
- Always show the Patient Alert Card to the doctor or nurse when you see them or if you go to hospital.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**



## 1. What YESCARTA is and what it is used for

YESCARTA is a type of medicine called a "genetically modified cell therapy".

YESCARTA is made specially for you as a single administration of your own modified white blood cells. It is given by a drip (*infusion*) into a vein (*intravenously*).

It is used to treat aggressive conditions in adults with diffuse large B-cell lymphoma (DLBCL) and primary mediastinal large B-cell lymphoma (PMBCL) affecting your lymph tissue (part of the immune system) that affects a type of white blood cell called B lymphocytes and other organs in your body. Too many of these abnormal white blood cells accumulate in your tissue and this is the cause of the symptoms you may have. It is used to treat these conditions when other available medicines have stopped working for you.

## 2. What you need to know before you are given YESCARTA

**You should not be given YESCARTA** if you are allergic to any of the ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.

**Warnings and precautions**

YESCARTA is made from your own white blood cells and should only be given to you.

**Before you are given YESCARTA you should tell your doctor if you:**
- have problems with your nervous system (such as fits, stroke, or memory loss).
- have kidney problems.

- have low blood cell levels (blood counts).
- have had a stem cell transplant in the last 4 months.
- have any lung, heart or blood pressure (low or raised) problems.
- have signs or symptoms of graft-versus-host disease. This happens when transplanted cells attack your body, causing symptoms such as rash, nausea, vomiting, diarrhoea and bloody stools.
- notice the symptoms of your cancer are getting worse. If you have lymphoma this might include fever, feeling weak, night sweats, sudden weight loss.
- have an infection. The infection will be treated before the YESCARTA infusion.
- have had hepatitis B, hepatitis C or human immunodeficiency virus (HIV) infection.

If any of the above apply to you (or you are not sure), talk to your doctor before being given YESCARTA.

**Tests and checks**
**Before you are given YESCARTA your doctor will:**
- Check your lungs, heart and blood pressure.
- Look for signs of infection; any infection will be treated before you are given YESCARTA.
- Check if your cancer is getting worse.
- Look for signs of graft-versus-host disease that can happen after a transplant.
- Check your blood for uric acid and for how many cancer cells there are in your blood. This will show if you are likely to develop a condition called tumour lysis syndrome. You may be given medicines to help prevent the condition.
- Check for hepatitis B, hepatitis C or HIV infection.
- Check if you had a vaccination in the previous 6 weeks or are planning to have one in the next few months.

**After you have been given YESCARTA**
**Tell your doctor or nurse immediately if you have any of the following:**
- Chills, extreme tiredness, weakness, dizziness, headache, cough, shortness of breath, or rapid heartbeat, which may be symptoms of a condition known as cytokine release syndrome. Take your temperature twice a day for 3-4 weeks after treatment with YESCARTA. If your temperature is high, see your doctor immediately.
- Fits, shaking, or difficulty speaking or slurred speech, loss of consciousness or decreased level of consciousness, confusion and disorientation, loss of balance or coordination.
- Fever, which may be a symptom of an infection.
- Extreme tiredness, weakness and shortness of breath, which may be symptoms of a lack of red blood cells.
- Bleeding or bruising more easily, which may be symptoms of low levels of cells in the blood known as platelets.

Your doctor will regularly check your blood counts as the number of blood cells and other blood components may decrease.

Do not donate blood, organs, tissues or cells for transplants.

If any of the above apply to you (or you are not sure), talk to your doctor or nurse before you are given YESCARTA. Your doctor may need to take special care of you during your treatment with YESCARTA.

In some cases, it might not be possible to go ahead with the planned treatment with YESCARTA. For example:

- If YESCARTA infusion is delayed for more than 2 weeks after you have received preparatory chemotherapy you may have to receive more preparative chemotherapy.

**Children and adolescents**

YESCARTA should not be used in children and adolescents below 18 years of age.

**Other medicines and YESCARTA**

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

Before you are given YESCARTA tell your doctor or nurse if you are taking any medicines that weaken your immune system such as corticosteroids, since these medicines may interfere with the effect of YESCARTA.

In particular, you must not be given certain vaccines called live vaccines:
- In the 6 weeks before you are given the short course of chemotherapy (called lymphodepleting chemotherapy) to prepare your body for the YESCARTA cells.
- During YESCARTA treatment.
- After treatment while the immune system is recovering.

Talk to your doctor if you need to have any vaccinations.

**Pregnancy and breast-feeding**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before being given this medicine. This is because the effects of YESCARTA in pregnant or breast-feeding women are not known, and it may harm your unborn baby or your breast-fed child.
- If you are pregnant or think you may be pregnant after treatment with YESCARTA, talk to your doctor immediately.
- You will be given a pregnancy test before treatment starts. YESCARTA should only be given if the results show you are not pregnant.

Discuss pregnancy with your doctor if you have received YESCARTA.

**Driving and using machines**
Some people may feel tired, dizzy or have some shaking after being given YESCARTA. If this happens to you, do not drive or use heavy machines until at least 8 weeks after infusion or until your doctor tells you that you have completely recovered.

**YESCARTA contains sodium**
This medicine contains 300 mg sodium (main component of cooking/table salt) in each infusion. This is the equivalent to 15% of the recommended maximum daily dietary intake of sodium for an adult.

## 3. How YESCARTA is given

YESCARTA will always be given to you by a healthcare professional.

- Since YESCARTA is made from your own white blood cells, your cells will be collected from you to prepare your medicine. Your doctor will take some of your blood using a catheter placed in your vein (a procedure call leukapheresis). Some of your white blood cells are separated from your blood and the rest of your blood is returned to your vein. This can take 3 to 6 hours and may need to be repeated.
- Your white blood cells are frozen and sent away to make YESCARTA. It usually takes about 3 to 4 weeks to receive your YESCARTA therapy but the time may vary.

**Medicines given before YESCARTA treatment**
During the 30 to 60 minutes before you are given YESCARTA you may be given other medicines. This is to help prevent infusion reactions and fever. These other medicines may include:
- Paracetamol.
- An antihistamine such as diphenhydramine.

Prior to receiving YESCARTA, you will be given other medicines such as preparative chemotherapy, which will allow your modified white blood cells in YESCARTA to multiply in your body when the medicine is given to you.

Your doctor or nurse will check carefully that this medicine is yours.

**How you are given YESCARTA**
- YESCARTA is a one-time treatment. It will not be given to you again.
- Your doctor or nurse will give you a single infusion of YESCARTA into your vein for approximately 30 minutes.
- YESCARTA is the genetically modified version of your white blood cells. Your healthcare professional handling YESCARTA will therefore take appropriate precautions (wearing gloves and glasses) to avoid potential transmission of infectious diseases and will follow local biosafety guidelines to clean up or dispose of any material that has been in contact with YESCARTA.

You must receive YESCARTA infusion in a qualified clinical facility and be discharged only when your doctor thinks it is safe for you to go home.
Your doctor may do blood tests to check for side effects.

**After you are given YESCARTA**
- Plan to stay within proximity from the hospital where you were treated for at least 4 weeks after you have been given YESCARTA. Your doctor will recommend that you return to the hospital daily for at least 10 days and will consider whether you need to stay at the hospital as an in-patient for the first 10 days after infusion. This is so your doctor can check if your treatment is working and help you if you have any side effects.

If you miss any appointments, call your doctor or the qualified clinical facility as soon as possible to reschedule your appointment.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

YESCARTA can cause side effects to your immune system that may be serious or life-threatening, and can lead to death.

The following side effects have been reported with YESCARTA.

**Very common (may affect more than 1 in 10 people)**
- Fever, chills, reduced blood pressure which may cause symptoms such as dizziness, lightheadedness, fluid in the lungs, which may be severe and can be fatal (all symptoms of a condition called cytokine release syndrome).
- Fever or chills.
- Decrease in the number of red blood cells (cells that carry oxygen) which may cause you to feel extremely tired with a loss of energy.
- Low blood pressure, dizziness.
- Feeling sick, constipation, diarrhoea, pain in the stomach or being sick.
- Headache, depressed level of consciousness, difficulty in speaking, agitation, shaking.

- Decrease in the number of white blood cells, which are important for fighting infections.
- Decreased levels of sodium, phosphate, or potassium which will show up on blood tests.
- Changes in the rhythm or rate of the heartbeat.
- Anxiety.
- Decrease in the number of cells that help clot the blood (thrombocytopenia).
- Infections in the blood caused by bacteria, viruses or other types of infection.
- Shortness of breath, cough.
- Low levels of antibodies called immunoglobulins, which may lead to infections.
- High blood pressure.
- Swelling in the limbs, fluid around the lungs (pleural effusion).
- Muscle and joint pain, back pain.
- Extreme tiredness.
- Dehydration.
- Decreased appetite, weight loss.
- Confusion.
- Increased levels of liver enzymes which will show up on blood tests.
- Dry mouth.
- Low oxygen level in blood.
- Pain in the hands or feet.

**Common (may affect up to 1 in 10 people)**

- Difficulty understanding numbers, memory loss, fits, loss of control of body movements.
- Failure of the kidneys causing your body to hold onto fluid which can be serious or life threatening.
- Fluid in the lungs.
- Lung infection.
- Sudden, unexpected stopping of the heart (cardiac arrest); this is serious and life-threatening.
- Heart failure.
- Muscle spasms.
- Difficulty to swallow.
- Leakage of fluids from blood vessels into surrounding tissue. This can lead to a weight gain and difficulty in breathing.
- Decreased levels of calcium which will show up on blood tests.
- Infections in the blood caused by fungi.
- Decreased levels of albumin which will show up on blood tests.
- Skin rash.
- Increased levels of bilirubin reporting on how your liver is working, which will show up on blood tests.
- Signs and symptoms of blood clots.
- Difficulty sleeping.
- Hypersensitivity.

**Uncommon (may affect up to 1 in 100 people)**

- Inflammation and swelling of spinal cord which may cause partial or total paralysis of limbs and torso.

Tell your doctor immediately if you get any of the side effects listed above. Do not try to treat your symptoms with other medicines on your own.

**Reporting of side effects**
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

## 5. How to store YESCARTA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the container label and infusion bag.

Store frozen in vapour phase of liquid nitrogen ≤ -150 °C until thawed for use.
Do not refreeze.

As this medicine will be given by qualified healthcare professionals, they are responsible for the correct disposal of the product. These measures will help protect the environment. This medicine contains genetically modified human blood cells. Local biosafety guidelines should be followed for unused medicine or waste material.

## 6. Contents of the pack and other information

**What YESCARTA contains**

The active substance is axicabtagene ciloleucel. Each patient-specific single infusion bag contains a dispersion of anti-CD19 CAR T cells in approximately 68 mL for a target dose of 2 x $10^6$ anti-CD19 CAR-positive viable T cells/kg.
The other ingredients (excipients) are: Cryostor CS10, sodium chloride, human albumin. See section 2 "YESCARTA contains sodium".

**What YESCARTA looks like and contents of the pack**

YESCARTA is a clear to opaque, white to red dispersion for infusion, supplied in an infusion bag individually packed in a metal cassette. A single infusion bag contains approximately 68 mL of cell dispersion.

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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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**This leaflet was last revised in**

**Other sources of information**

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

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**The following information is intended for healthcare professionals only:**

*Preparation of YESCARTA*

- Verify that the patient's identity (ID) matches the patient identifiers on the YESCARTA cassette.
- The YESCARTA product bag must not be removed from the cassette if the information on the patient-specific label does not match the intended patient.
- Once the patient's ID is confirmed, remove the YESCARTA product bag from the cassette.
- Check that the patient information on the cassette label matches that on the bag label.
- Inspect the product bag for any breaches of container integrity before thawing. If the bag is compromised, follow the local guidelines (or immediately contact Kite).
- Place the infusion bag inside a second sterile bag or per local guidelines.
- Thaw YESCARTA at approximately 37 °C using either a water bath or dry thaw method until there is no visible ice in the infusion bag. Gently mix the contents of the bag to disperse clumps of cellular material. If visible cell clumps remain, continue to gently mix the contents of the bag. Small clumps of cellular material should disperse with gentle manual mixing. YESCARTA should not be washed, spun down, and/or re-suspended in new media prior to infusion. Thawing should take approximately 3 to 5 minutes.
- Once thawed, YESCARTA is stable at room temperature (20 ˚C-25 ˚C) for up to 3 hours.

Do NOT use a leukodepleting filter.

All material that has been in contact with YESCARTA (solid and liquid waste) should be handled and disposed of as potentially infectious waste in accordance with local biosafety guidelines. Accordingly, healthcare professionals should take appropriate precautions (wearing gloves and glasses) when handling leukapheresis material or YESCARTA to avoid potential transmission of infectious diseases. Work surfaces and material which have potentially been in contact with YESCARTA must be decontaminated with appropriate disinfectant.

This medicine contains genetically modified human blood cells. Any unused medicine or waste material must be disposed of in accordance with local biosafety guidelines.

# ANNEX IV

# SCIENTIFIC CONCLUSIONS AND GROUNDS FOR THE VARIATION TO THE TERMS OF THE MARKETING AUTHORISATION(S)

**Scientific conclusions**

Taking into account the PRAC Assessment Report on the PSUR(s) for axicabtagene ciloleucel, the scientific conclusions of CHMP are as follows:

A causal relationship between spinal cord lesions and axicabtagene ciloleucel was confirmed, based on the evidence from two clinical trial cases; one case with an event of quadriplegia (in the setting of myelitis) and second case with events of muscular weakness and leukoencephalopathy, and one spontaneous case report with an event of spinal cord oedema. These events were considered as syndromes of neurologic toxicity, an important identified risk of axicabtagene ciloleucel use. Muscular weakness and leukoencephalopathy are listed in the axicabtagene ciloleucel product information. The PRAC considers that the product information of axicabtagene ciloleucel should be amended to reflect the risk of spinal cord oedema, myelitis and quadriplegia associated with axicabtagene ciloleucel therapy.

A causal relationship between dysphagia and axicabtagene ciloleucel was confirmed, based on the evidence from 15 post-marketing cases and 4 clinical trial cases of dysphagia. Dysphagia is a recognised symptom of encephalopathy which is currently listed in the product information; however, dysphagia can lead to serious complications and may require specific clinical measures. The PRAC considers that the product information of axicabtagene ciloleucel containing products should be amended to reflect the risk of dysphagia associated with axicabtagene ciloleucel therapy.

The CHMP agrees with the scientific conclusions made by the PRAC.

**Grounds for the variation to the terms of the marketing authorisation(s)**

On the basis of the scientific conclusions for axicabtagene ciloleucel the CHMP is of the opinion that the benefit-risk balance of the medicinal product(s) containing axicabtagene ciloleucel is unchanged subject to the proposed changes to the product information

The CHMP recommends that the terms of the marketing authorisation(s) should be varied.